Diastereoselective Synthesis of γ-Hydroxy-β-amino Alcohols and (2*S*,3*S*)-β-Hydroxyleucine from Chiral D-(*N*,*N*-Dibenzylamino)serine (TBDMS) Aldehyde

Taoues Laïb, Jacqueline Chastanet, and Jieping Zhu*

Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France

Received August 6, 1997

Introduction

Amino diols and β-hydroxy-α-amino acids are frequently found as key structural units in bioactive natural products. For instance, D-*erythro*-sphingosine (**1**)[1] (Figure 1) and its derivatives were shown to be important inhibitors of protein kinase C, a pivotal enzyme in cell regulation and signal transduction, while (2*S*,3*S*)-β-hydroxyleucine (**2**) is a key constituent of a range of natural peptide antibiotics such as telomycin,[2] azinothricin,[3] A83586C,[4] citropeptin,[5] variapeptin,[5] L-156602,[6] and verucopeptin[7] as well as a family of cyclopeptide alkaloids.[8] Amino alcohols in general also play an important role in modern organic chemistry as a class of versatile chiral ligands.[9] A number of elegant chemical syntheses including Sharpless asymmetric epoxidation (AE)/dihydroxylation (AD) methodology,[10] diastereoselective aldol condensation,[11] and chiral pool approach[12] among others[13] have been developed. All exhibit good levels of stereocontrol.[14] Leucine dehydrogenase from *Bacillus* species has also been employed for the enzymatic synthesis of L-β-hydroxyvaline.[15]

D-*erythro* sphingosine **1** (2*S*, 3*S*)-β-hydroxyleucine **2**

Figure 1.

As chiral building blocks, *N*-protected amino aldehydes have found numerous applications in the synthesis of a wide variety of compounds.[16] In this respect, *N*-protected serinal has special importance as the presence of a β-hydroxy group in the side chain of serine affords direct access to γ-hydroxy-β-amino alcohols and, moreover, provides a handle for further transformations. Several chiral serine aldehydes, in which the aldehyde group originates from the acid function of the amino acid, have been prepared. Thus, Garner and co-workers have developed a cyclic oxazolidine aldehyde (**3**),[17] (Figure 2) while Rapoport reported both an acyclic *N*-(phenylsulfonyl)- protected aldehyde (**4**)[18] and an *N*-(9-phenylfluoren-9-yl) cyclic carbamate (**5**).[19] Alternatively, Lajoie et al.[20] have disclosed an acyclic *N*-Fmoc serine aldehyde (**6**) in which the carboxylic function of serine is masked as an ortho ester and the hydroxy group is oxidized to an aldehyde function. These protected serine aldehydes are reactive toward a variety of classic reagents used for addition to the aldehyde function, and their synthetic potential has been amply demonstrated.[16] Among them,

(1) Hannun, Y. A.; Bell, R. M. *Science* **1989**, *243*, 500−507.
(2) Sheehan, J. C.; Maeda, K.; Sen, A. K.; Stock, J. A. *J. Am. Chem. Soc.* **1962**, *84*, 1303−05.
(3) Maehr, H.; Liu, C. M.; Palleroni, N. J.; Smallheer, J.; Todaro, L.; Williams, T. H.; Blount, J. F. *J. Antibiot.* **1986**, *39*, 17−25.
(4) Smitka, T. A.; Deeter, J. B.; Hunter, A. H.; Mertz, F. P.; Ellis, R. M.; Boeck, L. D.; Yao, R. C. *J. Antibiot.* **1988**, *41*, 726−733.
(5) Nakagawa, M.; Hayakawa, Y.; Furihata, K.; Seto, H. *J. Antibiot.* **1990**, *43*, 477−484.
(6) Hensens, O. D.; Borris, R. P.; Koupal, L. R.; Caldwell, C. G.; Currie, S. A.; Haidri, A. A.; Homnick, C. F.; Honeycutt, S. S.; Lindenmayer, S. M.; Schwartz, C. D.; Weissberger, B. A.; Woodruff, H. B.; Zink, D. L.; Zitano, L.; Fieldhouse, J. M.; Rollins, T.; Springer, M. S.; Springer, J. P. *J. Antibiot.* **1991**, *44*, 249−254.
(7) (a) Nishiyama, Y.; Sugawara, K.; Tomita, K.; Yamamoto, H.; Kamei, H.; Oki, T. *J. Antibiot.* **1993**, *46*, 921−927. (b) Sugawara, K.; Toda, S.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 928−935.
(8) (a) Joullié, M. J.; Nutt, R. E. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985, Vol. 3, p 113−168. (b) Schmidt, U.; Lieberknecht, A.; Haslinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, p 299−326.
(9) For recent reports on γ-hydroxy-β-amino alcohols, see: (a) Katsumura, S.; Yamamoto, N.; Morita, M.; Han, Q. *Tetrahedron: Asymmetry* **1994**, *5*, 161−164. (b) Vidal-Ferran, A.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970−82. For recent reviews, see: (c) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (d) Ajer, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 835−875.
(10) (a) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637−6640. (b) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256−261. (c) Caldwell, C. G.; Bondy, S, S. *Synthesis* **1990**, 34−36. (d) Sunazuka, T.; Nagamitsu, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A. Smith, A. B. *Tetrahedron Lett.* **1993**, *34*, 4447−4448. (e) Hale, K. J.; Manaviazar, S.; Delisser, V. M. *Tetrahedron* **1994**, *50*, 9181−9188. (f) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582−2583. (g) For a recent comprehensive review on AD, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.
(11) (a) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261. (b) Schöllkopf, U.; Beulshausen, T. *Liebigs Ann. Chem.* **1989**, 223−225. (c) Kanemasa, S.; Mori, T.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 8293−8296. (d) Evans, D A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761. (e) Zhu, J.; Bouillon, J. P.; Singh, G. P.; Chastanet, J.; Beugelmans, R. *Tetrahedron Lett.* **1995**, *36*, 7081−7084. (f) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470−3479 and references therein.
(12) (a) Garner, P.; Park, J. M.; Malecki, E. *J. Org. Chem.* **1988**, *53*, 4395−4398. (b) Reetz, R. M.; Drewes, M. W.; Lennick, K.; Schmidt, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375−378. (c) Murakami, T.; Minamikawa, H.; Hato, M. *Tetrahedron Lett.* **1994**, *35*, 745−748. Kozikowski, A. P.; Ding, Q. J.; Spiegel, S. *Tetrahedron Lett.* **1996**, *37*, 3279−3282.
(13) (a) Corey, E, J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735−38. (b) Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genêt, J. P. *Synlett* **1993**, 475−477. (c) Jackson, R. F.; Palmer, N. J.; Wythes, M. J.; Clegg, W.; Elsegood, M. R. J. *J. Org. Chem.* **1995**, *60*, 6431−6440. (d) Ciufolini, M. A.; Shimizu, T.; Swaminathan, S.; Xi, N. *Tetrahedron Lett.* **1997**, *38*, 4947−4950.
(14) For recent general reviews, see: (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (b) Durand, J. O.; Genêt, J. P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 612−619.
(15) Hanson, R. L.; Singh, J.; Kissick, T. P.; Patel, R. N.; Szarka, L. J.; Mueller, R. H. *Biorg. Chem.* **1990**, *18*, 116−130.
(16) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev. (Washington, D.C.)* **1989**, *89*, 149−164. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546.
(17) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361−2364. (b) Garner, P.; Park, J. M. *Org. Synth.* **1991**, *70*, 18−26.
(18) (a) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095−1098. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866−1875.
(19) Lubell, W.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824−3831.
(20) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021−5030.

S0022-3263(97)01468-0 CCC: $15.00
Published on Web 02/14/1998

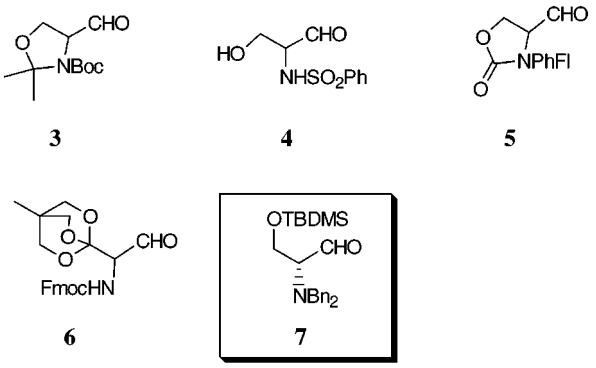
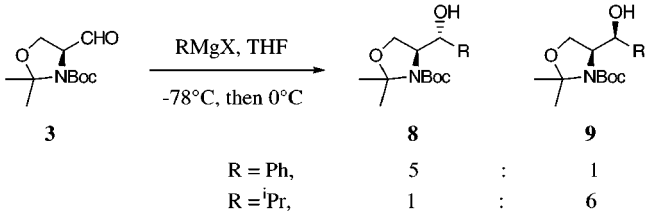


Figure 2.

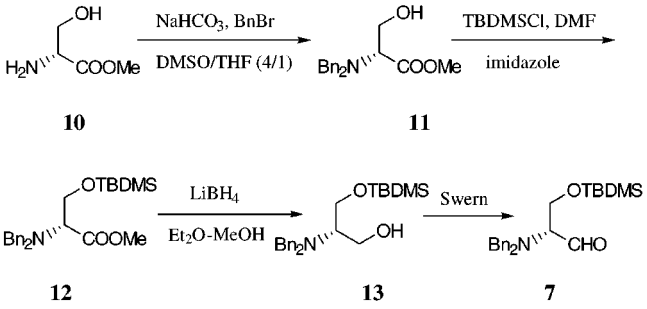
Scheme 1



Garner's aldehyde (**3**) is probably the most popular synthon and has been used as the starting material in the synthesis of a wide range of bioactive compounds.[16,21] Though moderate to good selectivities are generally obtained, the facial selectivity of addition of Grignard reagents and other organometallic species to this aldehyde has been shown to be reagent dependent. Moreover, both chelated and nonchelated processes can occur concomitantly, leading to diminished diastereoselectivity or even reversed facial selectivity such that prediction of stereochemical outcome is tenous (Scheme 1).[22]

In connection with our work on the total synthesis of cyclopeptide alkaloids,[23] we required an efficient and general synthesis of *erythro*-(2*S*,3*S*)-*β*-hydroxy-α-amino acids. Several years ago, Reetz[16b,24,25] introduced the concept of protecting-group tuning as a means of realizing high levels of asymmetric control in organometallic additions involving *N*,*N*-dibenzylamino aldehydes. Their configurational stability at room temperature and the reliable and predictable high diastereoselectivity (ds >90% is a rule) observed with a battery of different organometallics have made them a family of extremely useful chiral building blocks. Curiously, application of *N*,*N*-dibenzylserine aldehyde of type **7** (Figure 2) in asymmetric synthesis has scarcely been reported in the literature.[25,26] We report herein our studies concerning the synthesis of (2*R*)-2-(*N*,*N*-dibenzylamino)-3-*O*-[(*tert*-butyldimethylsilanyl)oxy]propionaldehyde (**7**) and its use for the asymmetric synthesis of amino diols and *β*-hydroxy-α-amino acids.[27]

Scheme 2



Results and Discussion

D-*N*,*N*-Dibenzylserine (TBDMS) aldehyde (**7**) was prepared as described in Scheme 2. Chemoselective bis *N*-benzylation of D-serine methyl ester (**10**) with benzyl bromide (DMSO−THF, $NaHCO_3$) gave the desired amino ester **11**, which was converted to TBDMS ether **12** under conventional conditions. Transformation of the ester to an aldehyde function was best realized in a two-step sequence. Thus, reduction of ester **12** with $LiBH_4$ in ether in the presence of methanol[28] gave the amino alcohol **13** in quantitative yield. No racemization due to silyl group migration was observed in the reduction step in accord with Meyers's observation.[29] Swern oxidation[30] of **13** then gave the desired amino aldehyde **7**. Though the oxidation proceeded cleanly, degradation of the aldehyde occurred during chromatographic purification leading to only moderate isolated yield (45−50%). That silica gel can catalyze the decomposition of *N*,*N*-dibenzylamino aldehyde has very recently been reported by Whiting, and a possible mechanism was proposed by the same group.[31] Thus, in the following studies, the crude aldehyde **7** obtained after conventional aqueous workup of the Swern oxidation reaction mixture was submitted directly to reaction with organometallic reagents.

Treatment of crude amino aldehyde **7** with 2 equiv of isopropylmagnesium chloride (Scheme 3) in THF gave the anti amino alcohol **14a** in 75% overall yield (two steps, 85−90% based on reacted starting material) together with the reduced product **13**. The Grignard addition is highly diastereoselective affording the anti product with a de greater than 95%. The stereochemistry

(21) For a recent application, see: Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 473−476. For a recent review concerning the use of amino acids as chiral pools, see: Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825−1872.

(22) (a) Williams, L.; Zhang, Z.; Ding, X.; Joullié, M. M. *Tetrahedron Lett.* **1995**, *36*, 7031−7034. (b) Han, B. H.; Kim, Y. C.; Park, M. K.; Park, J. H. *Heterocycles* **1995**, 1909−1914. (c) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673−11694.

(23) Zhu, J.; Laïb, T.; Chastanet, J.; Beugelmans, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2517−2519.

(24) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141−1143. For recent applications of Reetz's aldehydes, see: (b) Barluenga, J.; Baragana, B.; Concellon, J. M. *J. Org. Chem.* **1995**, *60*, 6696−6699. (c) Beaulieu, P. L.; Wernic D. *J. Org. Chem.* **1996**, *61*, 3635−3645. (d) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 351−352. (e) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 353−354. (f) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292−2297. (g) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293−4301 and references therein.

(25) For syn selective addition with diethylzinc see: Andrés, J. M.; Barrio, R.; Martinez M. A.; Pedrosa, R.; Pérez-Encabo, A. *J. Org. Chem.* **1996**, *1*, 4210−4213.

(26) *N*,*N*-Dibenzylserine (TBDMS) aldehyde (**7**) was mentioned in Reetz's review (ref 16b) on the basis of his unpublished results. Serine aldehydes wherein the side-chain hydroxy group was protected as a benzyl ether and a MOM ether were described in refs 12b and 25, respectively. See references therein.

(27) Part of this work has been published as a preliminary communication: Laïb, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1771−1772.

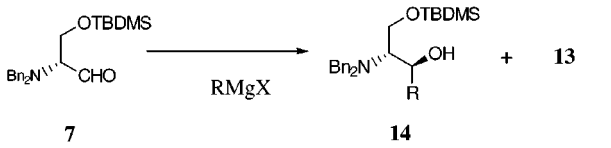
(28) Soai, K.; Ookawa, A.; Hayashi, H. *J. Chem. Soc., Chem. Commun.* **1983**, 668−669.

(29) Novachek, K. A.; Meyers, A. I. *Terahedron Lett.* **1996**, *37*, 1743−1746.

(30) Omura, K.; Swern, D. *Tetrahedron* **1978**, 1651−1660.

(31) Adia, M.; Hénaff, N.; Whiting, A. *Tetrahedron Lett.* **1997**, *38*, 3101−3102.

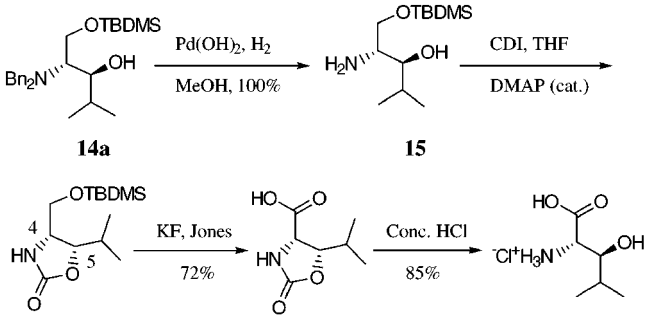
Scheme 3



7 14

entry 1	^{i}PrMgCl, THF	**14a** R = ^{i}Pr, 75%	10-15%
entry 2	^{i}PrMgCl, ether	**14a** R = ^{i}Pr, 88-95%	
		14b R = Me, 85%	
entry 3	MeMgBr, THF	**14c** R = Ph, 88%	
		14d R = Bu, 30%	
entry 4	PhMgBr, THF	**14d** R = Bu, 75%	
entry 5	BuLi, THF		
entry 6	$BuCeCl_2$, ether		

Scheme 4



14a **15** **16** **17** **2**

of **14a** was verified by its conversion into oxazolidinone **16** (Scheme 4, vide infra). The coupling constant (J_{H4-H5} = 6.5 Hz) together with the observation of an NOE cross-peak between the H-4 and H-5 protons of **16** indicated a cis relationship for these two protons and, thus, the anti stereochemistry of adduct **14a**.[32] It is appropriate to point out that the facial selectivity observed here is complementary to Joullié's observation that the syn product is formed predominantly when the same Grignard reagent is reacted with Garner's aldehyde (Scheme 1). The formation of the reduced product **13** may be explained by β-hydride elimination, frequently observed as a side product when both the substrate and the Grignard reagents are sterically hindered. We were able to overcome to a great extent this undesirable reaction pathway by simply running the reaction in diethyl ether instead of THF at −78 °C. Under these conditions, higher yields (88−95%) of desired product **14a** could be obtained. It is worth noting that in the case of Garner's aldehyde the stereochemical outcome is sensitive to the reaction medium and that diethyl ether favors the Cram chelating transition state leading to an increase in syn adduct formation.[22,33] However, in our case, the same degree of anti selectivity (within NMR detection limits) was observed in both THF and diethyl ether, indicating the strong preference for nucleophilic approach according to the Felkin−Anh model (vide infra).

Other Grignard reagents such as MeMgBr and PhMgBr reacted with **7** with equal efficiency to give the anti amino alcohols **14b** and **14c** in 85% and 88% yields, respectively. No reduced product **13** was isolated in these two cases as both reagents lack hydrogen atoms at the β position. The reaction of amino aldehyde **7** with alkyllithium gave a more complex reaction mixture from which the anti amino alcohol could be isolated, but only in less than 30% yield. However, when the organolithium reagent was transformed into an organocerium reagent,[34] the efficiency of the desired transformation was recovered to give the adduct **14d** in good chemical yield and with excellent anti diastereoselectivity. Reaction of **7** with the organocuprate reagent Bu_2CuLi was also attempted but results were less than satisfactory.[35]

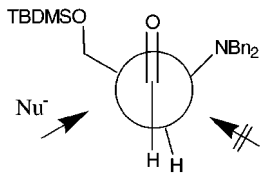


Figure 3.

One-pot Swern oxidation and in situ trapping of the resulting aldehyde with nucleophilic reagents, as developed by Ireland,[36] is known to be an excellent method to circumvent the deleterious side reactions characteristic of highly reactive carbonyl compounds. We applied this technique to the Swern oxidation medium (CH_2Cl_2) of **7** and found that addition of isopropylmagnesium chloride (5 equivalents) gave the desired amino alcohol **14a** with equal efficiency. A similar result was obtained when diethyl ether, instead of the usual CH_2Cl_2, was used as the solvent for the Swern oxidation.

The *tert*-butyldimethyl silyl group was selected as the protective group for the side-chain hydroxy group of serine mainly for its easy of introduction, its relative stability, and the nonchelating property of the resulting TBDMS ether. However, it is reasonable to postulate that the diastereoselectivity of the Grignard addition would be sensitive to the nature of the β-hydroxy protective group in the aldehyde **7**. We were thus concerned at the outset of this work that the bulky TBDMS protecting group would decrease the steric discrimination between the α-*N*,*N*-dibenzyl and α-CH_2OTBDMS groups, consequently decreasing the Felkin selectivity.[37] Experimentally, this was found not to be the case, and the excellent anti diastereoselectivity observed coincides nicely with the usual Felkin−Anh model (Figure 3).

The potential of this new chiral serine aldehyde derivative **7** is demonstrated by a highly diastereoselective synthesis of (2*S*,3*S*)-β-hydroxyleucine (**2**) as shown in Scheme 4. Hydrogenolysis of **14a** on Pearlman's catalyst gave amino alcohol **15**, which was transformed into oxazolidinone **16** by treatment with carbonyl diimidazole (CDI). One-pot deprotection and Jones oxidation[38]

(32) (a) Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308−3310. (b) Wagner, B.; Beugelmans, R. Zhu, J. *Tetrahedron Lett.* **1996**, *37*, 6557−6560.

(33) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697−1700.

(34) (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y. *J. Org. Chem.* **1984**, *49*, 3904−3912. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(35) The organolithium and organocuprate reagents are known to react cleanly with *N*,*N*-dibenzylalanine aldehyde; see ref 16b and: Reetz, M. T.; Reif, W.; Holdgrün, X. *Heterocycles* **1989**, *28*, 707−710.

(36) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198−2200.

(37) (a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199−2204. (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2204−2208.

(38) Liu, H. T.; Han, I. S. *Synth. Commun.* **1985**, *15*, 759−764.

led to the oxazolidinone carboxylic acid **17** in 72% yield. Finally, removal of the carbamate function under acidic conditions gave a quantitative yield of the hydrochloride salt of (2*S*,3*S*)-*β*-hydroxyleucine (**2**), whose physical data were identical in all respects with the literature values.[10]

In summary, reaction of *N*,*N*-dibenzylserine (TBDMS) aldehyde (**7**) with organometallic reagents shows an excellent diastereoselectivity. The anti selectivity observed is more predictable than with Garner's aldehyde and is complementary to that observed with Lajoie's synthon. The utility of this chiral building block has been demonstrated by a short synthesis of (2*S*,3*S*)-*β*-hydroxyleucine (**2**).

Experimental Section

General procedures and methods for characterization have been described previously.[39] Melting points are uncorrected.

(2*R*)-3-Hydroxy-2-(dibenzylamino)propionic Acid Methyl Ester (11). To a solution of D-serine methyl ester **10** (10.0 g, 64.3 mmol) in a mixture of THF (160 mL) and DMSO (40 mL) were added benzyl bromide (23.0 mL, 192.9 mmol) and $NaHCO_3$ (21.3 g, 253.6 mmol). The reaction mixture was heated to reflux for 15 h, cooled to room temperature, and diluted by addition of water. The aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 5/1 then 4/1) afforded compound **11** (19.2 g, quantitative): $[\alpha]_D = +138°$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3627, 3001, 2973, 2896, 1754, 1511, 1441, 1251, 1180, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.60−3.80 (m, 3H), 3.68, 3.92 (AB q, J = 13.4 Hz, 4H), 3.80 (s, 3H), 7.1−7.4 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 51.6, 54.9, 59.4, 61.8, 127.5, 128.6, 129.1, 138.7, 171.8; MS (EI) *m*/*z* 299, 268. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.02; H, 7.28; N, 4.44.

(2*R*)-3-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzyl)aminopropionic Acid Methyl Ester (12). To a solution of **11** (7.0 g, 23.4 mmol) in DMF (30 mL) were added imidazole (2.39 g, 35.1 mmol) and TBDMSCl (4.58 g, 30.4 mmol). After being stirred at room temperature under argon for 15 h, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 5/1) afforded TBDMS ether **12** (8.7 g, 90%): $[\alpha]_D = +42°$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3002, 2952, 2931, 2861, 1736, 1497, 1454, 1356, 1258, 1110, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (s, 6 H), 1.00 (s, 9H), 3.58 (t, J = 6.1 Hz, 1H), 3.70 (d, J = 14.1 Hz, 2H), 3.76 (s, 3H), 3.8−4.1 (m, 4H), 7.0−7.4 (m, 10H), ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5 18.2, 25.9, 26.1, 51.2, 55.5, 62.8, 63.0, 127.0, 128.3, 128.8, 140.0, 172.0; MS (CI) *m*/*z* 414 (M + 1). Anal. Calcd for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.52; N, 3.38. Found: C, 69.22; H, 8.36; N, 3.32.

(2*S*)-3-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)propan- 1-ol (13). To a solution of ester **12** (13.0 g, 31.5 mmol) in Et_2O (300 mL) were added $LiBH_4$ (2.8 g, 125.9 mmol) and MeOH (5 mL) at 0 °C. The reaction mixture was then heated to reflux for 3 h and quenched by addition of saturated NH_4Cl solution. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by filtration through a short pad of silica gel (eluent: heptane/EtOAc = 10/1) to give compound **13** (12.0 g, 99%): $[\alpha]_D = -64°$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3465, 2959, 2931, 2868, 1497, 1455, 1258, 1103 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.90 (s, 9H); 2.80 (brs, 1H, OH), 2.95 (m, 1H), 3.4−3.5 (m, 2H), 3.56 (d, J = 13.4, 2H), 3.65 (dd, J = 5.7, 10.6 Hz, 1H), 3.75 (dd, J = 6.1, 10.6 Hz, 1H), 3.81 (d, J = 13.4 Hz, 2H), 7.1−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −5.5, 18.2, 26.0, 54.1, 59.5, 59.7, 61.0, 127.1, 128.4, 129.0, 139.6; MS (CI) *m*/*z* 386 (M + 1). Anal. Calcd for $C_{23}H_{35}NO_2Si$: C, 71.64; H, 9.15; N, 3.63. Found: C, 71.21; H, 8.78; N, 3.54.

(2*R*)-3-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)propionaldehyde (7). To a cooled solution (−78 °C) of oxalyl chloride (140.4 μL, 1.62 mmol) in CH_2Cl_2 (3 mL) was added DMSO (252.8 μL, 3.56 mmol) dropwise. After 10 min, a solution of alcohol **13** (312 mg, 0.81 mmol) in CH_2Cl_2 was added in ca. 2 min. The reaction mixture was stirred for another 15 min, and TEA (1 mL, 7.3 mmol) was then added. After being stirred for 10 min at −78 °C, the cooling bath was removed and water was added at room temperature. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 10/1) afforded aldehyde **7** (138 mg, 45%): $[\alpha]_D = +7°$ (*c* 1.2, EtOAc); IR ($CHCl_3$) 2952, 2938, 2860, 1722, 1616, 1510, 1447, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.85 (s, 9H), 3.32 (t, J = 5.7 Hz, 1H), 3.82 (s, 4H), 3.98 (d, J = 5.7 Hz, 2H), 7.1−7.4 (m, 10H), 9.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5, 18.2, 26.0, 55.9, 60.1, 67.9, 127.3, 128.5, 128.9, 139.6, 203.5; MS (CI) *m*/*z* 384 $(M + 1)^+$. Compound **7** is unstable in $CHCl_3$ solution and should be kept in the refrigerator.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)-4-methylpentan-3-ol (14a). Oxidation of alcohol **13** (6.32 g, 16.4 mmol) was carried out under standard conditions as described above. Following the conventional workup procedure, the aqueous phase was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The crude aldehyde was dried in vacuo and was redissolved in diethyl ether (50 mL) and cooled to −78 °C. To this solution was added isopropylmagnesium chloride (2 M in THF, 16.4 mL, 32.8 mmol) dropwise. The reaction course was monitored by TLC, and once all the starting material (aldehyde) was consumed (1 h), the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 15/1 then 10/1) afforded the amino diol **14a** (6.12 g, 88%): $[\alpha]_D = -40°$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3693, 3062, 2412, 1600, 1462, 1118, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.40 (d, J = 6.6 Hz, 3H), 0.80 (s, 9H), 0.81 (d, J = 6.6 Hz, 3H), 1.95 (d of septet, J = 3.4, 6.6 Hz, 1H), 2.61 (dt, J = 5.0, 7.7 Hz, 1H), 2.70 (br s, 1H, OH), 3.45 (d, J = 13.7 Hz, 2H), 3.60 (dd, J = 3.4, 7.7 Hz, 1H), 3.75 (d, J = 13.7 Hz, 2H), 3.9−4.0 (m, 2H), 7.0−7.2 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.7, 15.6, 18.8, 21.1, 26.6, 30.5, 56.0, 59.5, 62.0, 78.1, 127.6, 129.0, 129.7, 130.0, 140.8; MS (CI) *m*/*z* 428 $(M + 1)^+$. Anal. Calcd for $C_{26}H_{41}NO_2Si$: C, 73.02; H, 9.66; N, 3.28. Found: C, 72.85; H, 9.77; N, 3.12.

Compounds **14b** and **14c** were prepared according to the same synthetic procedure described for the synthesis of **14a**.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)butan-3-ol (14b): $[\alpha]_D = -62°$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3456, 2973, 2937, 2854, 1609, 1510, 1469, 1456, 1357 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.95 (s, 9H), 1.28 (d, J = 6.8 Hz, 3H), 2.62 (td, J = 5.4, 7.0 Hz, 1H), 3.15 (br s, 1H, OH), 3.60, 3.90 (AB q, J = 13.7 Hz, 4H), 3.9−4.1 (m, 3H), 7.1−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.9, 18.1, 21.5, 25.8, 55.2, 61.3, 62.7, 68.7, 126.9, 128.3, 128.8, 139.8; MS (EI) *m*/*z* 399, 384, 354. Anal. Calcd for $C_{24}H_{37}NO_2Si$: C, 72.13; H, 9.27; N, 3.51. Found: C, 72.22; H, 9.09; N, 3.25.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)-3-phenylpropan-3-ol (14c): $[\alpha]_D = -15°$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3459, 3022, 2964, 2924, 2868, 1609, 1504, 1499, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.10 (s, 3H), 0.12 (s, 3H), 1.01 (s, 9H), 1.60 (brs, 1H, OH), 2.98 (td, J = 5.0, 7.1 Hz, 1H), 3.61, 3.72 (AB q, J = 13.7 Hz, 4H), 4.00 (d, J = 5.0 Hz, 2H), 4.98 (d, J = 7.1 Hz, 1H), 7.0−7.3 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −5.0, 18.2, 26.0, 55.3, 62.0, 62.5, 74.7, 126.9, 127.2, 127.4, 128.1, 128.3, 128.7, 128.8, 139.9, 143.4; MS (EI) *m*/*z* 461, 446, 404, 354. Anal. Calcd for $C_{29}H_{39}NO_2Si$: C, 75.44; H, 8.51; N, 3.03. Found: C, 75.24; H, 8.40; N, 2.80.

(2*R*,3*S*)-1-[(*tert*-Butyldimethylsilanyl)oxy]-2-(dibenzylamino)heptan-3-ol (14d). Cerium chloride ($CeCl_3 \cdot 7H_2O$) (480 mg, 1.3 mmol) was placed in a two-necked flask and was heated

(39) Beugelmans, R.; Singh, G. P.; Bois-Choussy, M.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1994**, *59*, 5535−5542.

in vacuo at 140 °C for 3 h until the weight became consistent to formula $CeCl_3$. After being cooled to room temperature, dry THF (5 mL) was added and cooled to −78 °C. To this suspension was added butyllithium (1.6 M in heptane, 812 μL) with stirring. Stirring was continued for another 1 h, and crude aldehyde obtained by standard Swern oxidation of alcohol **13** (231 mg, 0.6 mmol) in Et_2O (2 mL) was added. The reaction course was monitored by TLC, and once all the starting material (aldehyde) was consumed (2 h), the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 15/1 then 10/1) afforded the amino diol **14d** (198.5 mg, 75%): $[\alpha]_D = -43°$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) 3456, 2956, 2925, 2850, 1606, 1500, 1468, 1443, 1368, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 0.92 (t, *J* = 6.5 Hz, 3H), 1.2−1.4 (m, 5H), 1.75 (m, 1H), 2.65 (td, *J* = 5.4, 7.1 Hz, 1H), 3.0 (br s, 1H, OH), 3.62, 3.88 (AB q, *J* = 13.7 Hz, 4H), 3.90 (m, 1H), 4.00 (m, 2H), 7.0−7.3 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.9, 14.4, 18.4, 23.1, 26.2, 28.0, 35.0, 55.7, 61.5, 61.7, 72.6, 127.3, 128.6, 128.8, 140.4; MS (EI) *m*/*z* 441, 426, 384, 354. Anal. Calcd for $C_{27}H_{43}NO_2Si$: C, 73.47; H, 9.81; N, 3.17. Found: C, 73.77; H, 9.73; N, 3.47.

(4*R*,5*S*)-4-[(*tert*-Butyldimethylsilanyl)oxy]methyl]-5-isopropyloxazolidin-2-one (16). A solution of compound **14a** (1.03 g, 2.41 mmol) in methanol was hydrogenated in the presence of 10% of Pearlman's catalyst [$Pd(OH)_2$] at 1 atm. After being stirred vigorously for 1 h, the reaction mixture was filtered through a short pad of Celite and washed thoroughly with MeOH. The filtrate was evaporated to give compound **15**, which was used without further purification: $[\alpha]_D = +10°$ (*c* 0.5, MeOH); IR ($CHCl_3$) 3690, 3466, 2397, 1602, 1236, 843 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 0.10 (s, 6H), 0.9−1.0 (m, 15H), 1.85 (m, 1H), 2.80 (ddd, *J* = 3.8, 6.7, 7.8 Hz, 1H), 3.19 (dd, *J* = 5.3, 6.7 Hz, 1H), 3.52 (dd, *J* = 7.8, 9.8, 1H), 3.85 (dd, *J* = 3.8, 9.8 Hz, 1H); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6H), 0.87 (s, 9H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 1.75 (septet, *J* = 6.6 Hz, 1H), 2.98 (dt, *J* = 4.4, 6.7 Hz, 1H), 3.1−3.2 (m, 4H, 1CH + NH_2 + OH), 3.63 (dd, *J* = 6.7, 10.1 Hz), 3.69 (dd, *J* = 4.2, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.0, 18.6, 19.2, 25.9, 30.5, 53.5, 64.2, 79.0; MS (EI) *m*/*z* 232 $[M - 15]^+$, 204, 190. To the solution of so obtained amino alcohol in THF were added carbonyldiimidazole (CDI, 507.5 mg, 3.13 mmol) and a catalytic amount of DMAP (0.24 mol, 29.4 mg). After being stirred at room temperature for 15 h, the reaction mixture was diluted with saturated aqueous NH_4Cl solution. The aqueous solution was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (eluent: heptane/EtOAc = 3/1 then 2/1) afforded the oxazolidinone **16** (559.2 mg, 85%): $[\alpha]_D = +65°$ (*c* 0.2, $CHCl_3$); IR ($CHCl_3$) 3683, 2960, 2931, 1757, 1468, 1391, 1103, 836 cm^{-1}; ^1H NMR (C_6D_6, 250 MHz) δ −0.05 (s, 3H), −0.04 (s, 3H), 0.48 (d, *J* = 6.6 Hz, 3H), 0.82 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H), 1.85 (d of septet, *J* = 6.6, 10.4 Hz, 1H), 3.01 (m, 1H), 3.21 (dd, *J* = 5.9, 10.4 Hz, 1H), 3.22 (dd, *J* = 4.9, 10.4 Hz, 1H), 3.58 (dd, *J* = 6.5, 10.4 Hz, 1H), 5.35 (brs, 1H, NH); ^1H NMR ($CDCl_3$, 250 MHz) δ −0.05 (s, 6H), 0.88 (s, 9H), 0.99 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.9−2.0 (m, 1H), 3.51 (dd, *J* = 8.7, 10.5 Hz, 1H), 3.6−3.8 (m, 2H), 4.08 (dd, *J* = 6.2, 10.5 Hz, 1H), 5.4 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.2, 19.0, 19.9, 25.9, 27.5, 56.7, 61.5, 84.4, 161.0; MS (CI) *m*/*z* 274 $[M + 1]^+$, 259. Anal. Calcd for $C_{13}H_{27}NO_3Si$: C, 57.10; H, 9.95; N, 5.12. Found: C, 56.87; H, 9.62; N, 5.36.

(4*S*,5*S*)-5-Isopropyl-2-oxooxazolidine-4-carboxylic Acid (17). To a solution of compound **16** (311 mg, 1.14 mmol) in acetone (5 mL), cooled at 0 °C, was added potassium fluoride (132 mg, 2.28 mmol) and Jones reagent (8 N, 853 mL). After being stirred at 0 °C for 6 h, the reaction was quenched by dropwise addition of 2-propanol at the same temperature, and stirring was continued for another 30 min. The reaction mixture was diluted with saturated $NaHCO_3$ solution, the volatiles were removed in vacuo, and the aqueous phase was extracted with EtOAc to remove all the neutral species. The aqueous phase was then acidified to pH = 2 and extracted again with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give analytically pure acid **17** (142 mg, 72%): mp 170 °C; $[\alpha]_D = +16.1°$ (*c* 0.18, MeOH) [lit.[10b] = +16.9 (*c* 1.95, MeOH)]; ^1H NMR (CD_3OD, 200 MHz) δ 1.02 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.95 (m, 1H), 4.40 (m, 2H); ^{13}C NMR (CD_3OD, 250 MHz) 19.4, 30.8, 59.6, 85.8, 162.5, 173.2; MS (CI) *m*/*z* 174 $[M + 1]^+$. Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.08. Found: C, 48.41; H, 6.26; N, 7.86.

(2*S*,3*S*)-β-Hydroxyleucine (2). A solution of compound **17** (500 mg, 2.89 mmol) in concentrated HCl (20 mL) was refluxed for 40 h, and evaporation of the volatile gave pure product **2** as hydrochloride salt (453 mg, 85%): $[\alpha]_D = +39°$ (*c* 0.1 H_2O), [lit.[10c] = +37° (*c* 0.9, 1 N HCl)]; IR (KBr) 3130−3160, 1740, 1647 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 0.95 (d, *J* = 6.5 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 2.04 (m, 1H), 3.42 (dd, *J* = 8.5, 2.8 Hz, 1H), 4.01 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ 19.4, 20.0, 32.0, 56.8, 77.5, 169.5; MS (CI) *m*/*z* 149 $[M + 1]^+$.

Acknowledgment. Financial support from the CNRS and a doctoral fellowship from "Ligue National Contre le Cancer" to T.L. are gratefully acknowledged.

Supporting Information Available: ^1H NMR spectra of compounds **2**, **7**, **13**, and **15** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page of ordering information.

JO971468W